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10/695,680	10/29/2003	James Frederick Harrington JR.	21486-056	5034

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EXAMINER

RAMACHANDRAN, UMAMAHESWARI

ART UNIT	PAPER NUMBER
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1617

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08/04/2009

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/695,680	Applicant(s) HARRINGTON, JAMES FREDERICK	
	Examiner UMAMAHESWARI RAMACHANDRAN	Art Unit 1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 08 May 0209.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-13 and 21 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-13 and 21 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/8/2009 has been entered.

Claim 1 has been amended and claims 14-20, 22 have been cancelled. Claims 1-13 and 21 are currently pending and are being examined on the merits herein.

Response to Remarks/Arguments

Applicants' remarks and arguments regarding the 103(a) rejections have been fully considered but are moot in view of new rejections presented in this action. Applicants' amendments, further search and consideration necessitated the new rejections presented in this office action. Accordingly, the action is made non-final.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 9, 11-13, 21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The specification teaches how to evaluate human responses to glutamate antagonist treatment (para 0043), specific methods of animal models in pain including implantation of an Epidural Alzet

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Miniosmotic Trump for Epidural Infusion and Placement of Foraminal Stents, behavioral tests (Von-Frey Fiber testing), compounds and peptides that are useful to inhibit binding of free glutamate from cartilage degradation in disc or joint tissue from binding to glutamate receptors on nerve cells (para 0055-60). The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

(1, 5) *The nature of the invention and the breadth of the claims:*

The instant claims are directed to a method of alleviating back pain in a mammal, comprising contacting a neuronal cell of cartilaginous tissue with a glutamate receptor antagonist injected directly to intervertebral disc tissue. The claims are broad with respect to the glutamate receptor antagonist compounds. The dependent claims (6, 7, 10) are limited to specific glutamate receptor antagonists.

(3) *The relative skill of those in the art:*

The relative skill of those in the pharmaceutical and medical arts is high, requiring advanced education and training.

(2) *The state of the prior art:*

According to the wikipedia document, Glutamate receptor, there are different types of glutamate receptors, NMDA, non-NMDA, kainite, AMPA and mGluR (ionotropic and metabotropic) (http://en.wikipedia.org/wiki/Glutamate_receptor). There are at least

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two variants of NMDA receptor types (NR1 and NR2) (http://en.wikipedia.org/wiki/NMDA_receptor). The metabotropic glutamate receptor can be classified into eight different types (http://en.wikipedia.org/wiki/Metabotropic_glutamate_receptor). The prior art Allgeier et al. (U.S. 2001/0056084) teaches the use of selective mGluR5 antagonists for the treatment of pain including trigeminal or herpetic neuralgia, diabetic neuropathic pain, low back pain etc (see Abstract, para 0032). The prior art Cherry et al. (Pain, 62, 119-121, 1995) teaches ketamine as an adjunct to morphine in the treatment of pain. In summary, prior art teaches the four different types of glutamate receptors and several subtypes of the receptors. Williams et al. (US 2003/0082214) teaches NMDA receptor antagonists in treatment of pain (see abstract, claims) and teaches MK-801 as one of the NMDA receptor antagonists useful for the treatment. In summary, a number of antagonists exist for each type of the glutamate receptor and subtype of the receptor and the prior art teaches the benefits of glutamate receptor antagonists in treating back pain.

(4) *The predictability of the art:*

Despite the advance training of those in the art, the art is highly unpredictable. It is still not possible to predict the pharmacological activity or treatment efficacy of a compound based on the structure alone. It is also not possible to predict the efficacy of a given class of compounds for the treatment of a particular disease absent a mechanistic link between the pharmacological activity of the class of agents and the etiology or pathophysiology of the disease. Typically, in order to verify that a compound will be effective in treating a disease, the compounds must be either tested directly in a

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patient or in a model that has been established as being predictive of treatment efficacy.

In order to predict whether a class of compounds would be effective in treating a disease, the etiology or pathophysiology of the disease must be uncovered, and there should be a nexus between the pharmacological activity of the class of agents and the etiology or pathophysiology of the disease. Even if the mechanism is defined for a particular class of drugs it is not predictable from such studies that each drug that falls into the class will be useful in treating the condition without any severe adverse or side effects. Applicants' claim administration of glutamate receptor antagonists in a method of alleviating back pain. The claims are very broad with respect to the glutamate receptor antagonist compounds known and yet to be discovered. There could be drug interactions of glutamate receptor antagonists with other compounds. For example, MK-801 has drug interaction with clonidine. Also, several of the glutamate receptor antagonists are associated with side effects. Amantadine has been associated with several central nervous system side effects (<http://en.wikipedia.org/wiki/Amantadine>). Some of the side effects of dextromethorphan include cardiac arrest, body rash/itching, blurred vision, urinary retention, hypertension etc. (<http://en.wikipedia.org/wiki/Dextromethorphan>). Long term side effects of ketamine include cognitive impairments including memory problems (<http://en.wikipedia.org/wiki/Ketamine>). Though it is known in the art that ketamine, glutamate receptor antagonist and mGluR antagonists in a method of treating back pain it is not predictable from the prior art and from the Applicants' teachings that every single glutamate receptor antagonist claimed would be useful in a method of treating back pain.

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(6, 7) *The amount of guidance presented and the presence of working examples:*

It has been established that, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." *In re Fisher*, 427 F.2d 833, 839 166 USPQ 18, 24 (CCPA 1970). Applicant has given guidance towards how to evaluate human responses to glutamate antagonist treatment (para 0043), specific methods of animal models in pain including implantation of an Epidural Alzet Miniosmotic Pump for Epidural Infusion and Placement of Foraminal Stents, behavioral tests (Von-Frey Fiber testing), compounds and peptides that are useful to inhibit binding of free glutamate from cartilage degradation in disc or joint tissue from binding to glutamate receptors on nerve cells (para 0055-60). The prior art teaches the use of glutamate receptor antagonists such as mGluR5 antagonists in treating back pain and Cherry et al. teaches the use of ketamine as an adjunct therapy for treating back pain. Also, it is known in the art that NMDA receptor antagonists are useful in treating pain.

(8) *The quantity of experimentation needed:*

In order to enable the instantly claimed methods commensurate with the entire scope, a large quantity of experimentation would be necessary. With Applicants' guidance provided in the specification and what is known in the prior art the person of ordinary skill in the art would have to conduct experiments testing at least few of each of the receptor antagonists for treating back pain. In order to practice the above claimed invention, one of ordinary skill in the art would have to first envision formulation, dosage, duration, route and, in the case of human treatment, an appropriate animal model

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system to test all the glutamate receptor antagonist compounds to determine whether or not they are useful in treating the back pain. If unsuccessful, one of ordinary skill in the art would have to envision a modification in the formulation, dosage, duration, route of administration etc. and appropriate animal model system, or envision an entirely new combination of the above and test the system again. Considering the number and type of glutamate receptors (known and yet to be discovered) a large number of antagonists need to be tested in vitro and then in vivo to determine the therapeutic benefits in treatment of back pain in a mammal. Also, unpredictability is involved due to the drug interactions, adverse and side effects and this would be an arduous and daunting task. Considering the above-mentioned factors and the fact that there are significant inter-individual variability in using a pharmacological modalities in human subjects, the nature of art is unpredictable, and the breadth of the claims; one of ordinary skill in the art would be burdened with undue "experimentation study" to determine which glutamate receptor antagonist compounds would be useful in treating back pain. Therefore, it would require undue, unpredictable experimentation to practice the claimed invention of a method of treating back pain in a mammal comprising administering a glutamate receptor antagonist. *Genetech*, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable". Accordingly, the entire scope of the instant claims is not enabled.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 12 recites the limitation “method in claim 1, wherein said pain is selected from the group consisting of back pain, joint pain, and sciatic pain” in lines 1-2. There is insufficient antecedent basis for this limitation in the claim. Claim 1 is towards a method of treating back pain in a mammal. However, claim 12 has limitations of treating joint pain, sciatic pain. Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-5, 9, 12, 13, 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over NewsRx Article (Pain & Central Nervous System Week, via

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NewsRx.com, July, 2000) and Zhou (Vol. 7, 4, Feb 2002) in view of Ausman et al. (US 4,039,682).

The NewsRx article teaches that free glutamate resulting from lumbar disc degradation may be the source of low back pain in patients with herniated lumbar discs. The reference teaches that Harrington et al. hypothesized that when proteoglycan disc protein are broken down by enzymes in the lumbar area, where no reuptake mechanisms are present, they are able to make their way to the dorsal root ganglion where they set off glutamate receptors and further teach that glutamate originating from degenerated disc proteoglycan may diffuse to the dorsal root ganglion and effect glutamate receptors. In summary, the reference teaches that back pain in patients with herniated lumbar discs may be caused by free glutamate resulting from herniated disc degradation, rather than pressure on nerves caused by the herniation.

Zhuo teaches glutamate as a sensory transmitter for pain and further teach that antagonism of both kainate and AMPA receptors (glutamate receptors) yields greater analgesic effects in adult animals than AMPA receptor antagonism alone (p 259, col. 2, para 2, lines 9-12, last two lines, p 260, col. 1, para 1, lines 1-2) and NMDA receptors have a crucial role in chronic pain (p 265, col. 1, para 1, lines 19-20). Table 2 of the reference illustrates the pain medicines currently used in hyperalgesia, allodynia and neuropathic pain and that includes glutamate receptor antagonists such as AMPA/kainite receptor antagonists, NMDA receptor antagonists.

It would have been obvious to one having ordinary skill in the art at the time of the invention from the above cited prior art teachings that back pain in patients with

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herniated lumbar discs may be caused by free glutamate resulting from herniated disc degradation and administration of glutamate receptor antagonists would be useful in treating pain including back pain.

The references do not explicitly teach administration of glutamate receptor antagonists into intervertebral disc tissue to inhibit binding of said free glutamate to said glutamate receptors.

Ausman et al. teaches a method of relieving back pain and related symptoms comprising injecting drugs into an intervertebral disk of the back (see abstract, claims). It would have been obvious to one having ordinary skill in the art at the time of the invention to have injected drugs into an intervertebral disk tissue because Ausman teaches it is a common and successful procedure to inject effective dosages of drugs into an intervertebral disk of the back to relieve pain. Annulus tears can be a precursor of herniated disc or damage by tear can cause herniated disc. Also, it is known in the art that administration of drugs, a part of dosage regimen is an element that can be routinely optimized. The type of administration is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal amount of ingredient to add in order to best achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, this optimization of ingredient amount would have been obvious at the time of applicant's invention. The references do not explicitly teach that administration of the agent

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comprises contacting a neuronal cell of a cartilaginous tissue with the agent. However, it would be obvious to a person of ordinary skill in the art that injection of an agent at the intervertebral disc comprises contacting a neuronal cell of a cartilaginous tissue.

Claims 6, 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over NewsRx Article (Pain & Central Nervous System Week, via NewsRx.com, July, 2000) and Zhou (Vol. 7, 4, Feb 2002) in view of Ausman et al. (US 4,039,682) as applied to claims 1-5, 9, 12, 13, 21 above and further in view of Lawand et al. (Euro J of Pharmacology, 324, (1997), 169-177).

The teachings of NewsRx article, Zhou, Ausman et al. as discussed as above.

The references do not teach the specific antagonists claimed in claims 6 and 7 in treating back pain.

Lawand et al. teaches the intra-articular injection in knee joint of either an NMDA or a non-NMDA glutamate receptor (CNQX) attenuated the thermal hyperalgesia and the mechanical allodynia produced by glutamate, arginine and aspartate (see Abstract). This addresses claims 2-4, 7, 12, 15, 16 and 20. The reference also teaches that the administration of MK-801 reduced the induced thermal hyperalgesic response (p 174, col. 2, lines 26-27) and thus addresses claims 5 and 6. The reference further teaches that attenuation of pain related behavior by intra-articular application of NMDA and non-NMDA excitatory amino acid antagonists after full development of the knee joint inflammation suggests a novel and viable alternative for pharmacological reduction of joint pain associated with inflammation (p 177, col. 2-7).

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It would have been obvious to one of ordinary skill in the art at the time of the invention to administer ionotropic glutamate receptor or NMDA type receptor antagonist such as MK-801 or an AMPA receptor antagonist such as CNQX in a method to alleviate back pain in mammal. The motivation to do so is taught by the prior art teachings cited above and Lawland et al. It would have been obvious from the teachings of NewsRx document and Zhou teaches that back pain in patients with herniated lumbar discs may be caused by free glutamate resulting from herniated disc degradation and administration of glutamate receptor antagonists would be useful in treating pain including back pain. Lawland teach that intra-articular injection in knee joint of either an NMDA (MK-801) or a non-NMDA glutamate receptor (CNQX) attenuated the thermal hyperalgesia and the mechanical allodynia produced by glutamate. Hence one of ordinary skill in the art would have been motivated to administer such compounds to alleviate back pain by inhibition of binding of free glutamate released to alleviate back pain.

Claims 8, 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over NewsRx Article (Pain & Central Nervous System Week, via NewsRx.com, July, 2000) and Zhou (Vol. 7, 4, Feb 2002) in view of Ausman et al. (US 4,039,682) as applied to claims 1-5, 9, 12, 13, 21 above and further in view of Stanfa et al. (Neuroscience, 1999, vol. 93, No. 4, p 1391-1398).

The teachings of NewsRx article, Zhou, Ausman et al. as discussed as above.

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The references do not teach a method of alleviating pain by administering the specific KA receptor antagonists claimed and binding of free glutamate to mGlu2 receptor.

Stanfa et al. teaches the administration of non-NMDA receptor antagonists NBQX (AMPA, Glu R1-4 subunit) and LY383884, a KA receptor antagonist directly to the spinal cord of rats (col. 1, p 1392). The reference teaches the enhanced role of AMPA and Kainate antagonists in spinal nociceptive processing in inflammatory states (see Abstract) thus addressing claims 8 and 11.

It would have been obvious to one of ordinary skill in the art to use KA receptor antagonists in a method of treatment to alleviate pain. The motivation to do is provided from the prior art teachings of NewsRx document, Zhou and Stanfa et al. As stated above, it would have been obvious from the teachings of NewsRx document and Zhou teaches that back pain in patients with herniated lumbar discs may be caused by free glutamate resulting from herniated disc degradation and administration of glutamate receptor antagonists would be useful in treating pain including back pain. Stanfa et al. teaches the enhanced role of AMPA and Kainate antagonists in spinal nociceptive processing in inflammatory states. Hence one of ordinary skill in the art would have been motivated to administer a KA receptor antagonist compound such as LY383884 to alleviate back pain by inhibition of binding of free glutamate released in conditions like herniated disc.

Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over NewsRx Article (Pain & Central Nervous System Week, via NewsRx.com, July, 2000) and Zhou

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(Vol. 7, 4, Feb 2002) in view of Ausman et al. (US 4,039,682) as applied to claims 1-5, 9, 12, 13, 21 above and further in view of Garrett (Biol. Res. for Nursing, Vol. 1, No. 4, Apr 2000).

The teachings of NewsRx article, Zhou, Ausman et al. as discussed as above.

The references do not teach a method of alleviating pain by administering the specific metabotropic glutamate receptor antagonists as claimed in claim 10.

Garrett teaches that L-AP3 a metabotropic glutamate receptor antagonist exhibited an antinociceptive effect in animals linking effective treatment of hyperalgesia with metabotropic glutamate receptor (p 316, col. 2, lines 5-9). This addresses claims 9 and 10.

It would have been obvious to one of ordinary skill in the art to use metabotropic glutamate receptor antagonists in a method of treatment to alleviate pain. The motivation to do is provided by NewsRx document, Zhou and Garrett. As stated above, it would have been obvious from the teachings of NewsRx document and Zhou teaches that back pain in patients with herniated lumbar discs may be caused by free glutamate resulting from herniated disc degradation and administration of glutamate receptor antagonists would be useful in treating pain including back pain. Garrett teaches the crucial role of excitatory amino acid, glutamate, NMDA and non-NMDA receptors in pain transmission, pain modulation, central sensitization and the sensation of hyperalgesia (see Abstract, p 311, col. 1, lines 15-44). The reference further teaches that L-AP3 a metabotropic glutamate receptor antagonist exhibited an antinociceptive effect in animals linking effective treatment of hyperalgesia. Hence one of ordinary skill in the art

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would have been motivated to administer a metabotropic glutamate receptor antagonist such as L-AP3 in conditions like degenerated disc to alleviate back pain by inhibition of binding of free glutamate released in conditions like herniated disc.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to UMAMAHESWARI RAMACHANDRAN whose telephone number is (571)272-9926. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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